

Prognostic value of combined lymphocyte-to-monocyte ratio and cancer antigen 724 in patients with proximal gastric cancer residing in extremely cold regions

Xiqing Zhu^{1#}, Dali Li^{2#}, Shanshan Liang^{3#}, Huaxing Wu^{4*}, Haibin Song^{1*}

Abstract

Background: This study aimed to evaluate the prognostic value of the lymphocyte-to-monocyte ratio (LMR) and cancer antigen 724 (CA724) in patients with proximal gastric cancer residing in cold climate regions. **Methods:** A retrospective analysis was conducted on 313 patients diagnosed with proximal gastric cancer in cold climate regions between 2014 and 2017. Preoperative hematological markers, including LMR and CA724, were assessed. Receiver operating characteristic (ROC) curves were used to determine optimal cutoff values, which were then combined to form the LMR + CA724 score. Statistical analyses included Kaplan-Meier survival curves, log-rank tests, and Cox proportional hazards regression. **Results:** A high preoperative LMR + CA724 score was significantly associated with older age, advanced pTNM stage, vascular invasion, and elevated levels of NMPVR, NMR, and AAR. The LMR + CA724 score demonstrated a higher area under the curve (AUC) compared to LMR or CA724 alone. Multivariate analysis identified pTNM stage, Borrmann type, histological type, and the LMR + CA724 score as independent prognostic factors for overall survival (OS). A nomogram incorporating these four variables achieved an AUC of 0.817, indicating strong predictive performance. **Conclusion:** The LMR + CA724 score is a reliable and independent prognostic indicator for patients with proximal gastric cancer in cold climate regions. Its integration into clinical practice may support treatment planning and long-term management by enhancing personalized care. Further prospective studies are warranted to validate these findings in broader and more diverse patient populations.

Keywords

proximal gastric cancer; cold regions; lymphocyte-to-monocyte ratio; carbohydrate antigen 724; prognostic evaluation

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1 Introduction

Gastric cancer remains one of the five most commonly diagnosed cancers worldwide and ranks as the fourth leading cause of cancer-related mortality^[1]. Due to the often subtle or absent symptoms in its early stages, many patients are diagnosed only after the disease has progressed. Although radical resection followed by adjuvant chemotherapy has become the standard treatment for gastric cancer, a significant proportion of patients still experience recurrence and metastasis, resulting in poor long-term survival outcomes^[2].

In recent years, the incidence of distal gastric cancer has

declined in many Western countries, whereas the incidence of proximal gastric cancer has continued to rise^[3-5]. Studies have shown that proximal and distal gastric cancers exhibit distinct biological behaviors and clinical characteristics, with proximal tumors associated with a poorer prognosis^[6]. Because of its higher malignancy and worse outcomes, proximal gastric cancer requires individualized treatment strategies and reliable prognostic biomarkers to support clinical decision-making.

At present, the TNM staging system remains the most widely utilized tool for assessing prognosis and guiding treatment in gastric cancer^[7]. However, TNM staging alone may be insufficient for accurate prognostic evaluation, particularly in patients with

proximal gastric cancer. To enhance prognostic stratification and complement existing staging systems, researchers have explored a variety of additional predictive indicators.

Among these, systemic inflammatory responses have been recognized as important contributors to tumor development and progression. Recent studies have highlighted several readily measurable inflammatory markers derived from routine blood tests that are associated with gastric cancer prognosis. These include the lymphocyte-to-monocyte ratio (LMR)^[8], the hemoglobin, albumin, lymphocyte and platelet (HALP) score^[9], and the glucose-to-lymphocyte ratio^[10]. In addition, tumor markers are widely used in clinical practice to evaluate recurrence risk and long-term outcomes.

In extremely cold regions, environmental and lifestyle factors such as climate conditions, dietary habits, and cultural practices may influence the epidemiology and prognosis of gastric cancer. Notably, the consumption of high-salt and pickled foods—commonly seen in cold climates—has been identified as a significant risk factor for gastric cancer^[11]. In this study, we focused on patients from a cold climate region diagnosed with proximal gastric cancer. Our objective was to investigate the prognostic value of preoperative hematological markers, including LMR and cancer antigen 724 (CA724), in order to improve prognostic assessment and support the development of personalized treatment strategies for these patients.

2 Patients and methods

A total of 313 patients diagnosed with gastric fundus cancer who underwent gastrectomy at Harbin Medical University Cancer Hospital between January 2014 and December 2017 were retrospectively enrolled in this study. The inclusion criteria were as follows: (1) residency in extremely cold regions for an extended period; (2) no chemotherapy and/or radiotherapy prior to surgery; (3) primary tumor located in the gastric fundus; (4) no history of other malignant tumors; and (5) survival for at least one month postoperatively. Demographic data, preoperative laboratory findings, surgical records, and pathological characteristics were systematically collected. Staging was classified according to the 8th edition of the TNM classification by the UICC/AJCC. The study was approved by the Ethics Committee of Harbin Medical University (2019-164-R) and conducted in accordance with the Declaration of Helsinki. All patients included in this study have signed written informed consent.

2.1 Collection and calculation of cancer-related inflammation indicators

Fasting peripheral blood samples were collected within one week

prior to surgery for hematological and biochemical analysis. The following parameters were measured: lymphocytes, neutrophils, monocytes, hemoglobin, platelets, mean platelet volume (MPV), red cell distribution width (RDW), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), glucose, plasma fibrinogen, and CA724.

The following indices were calculated based on these parameters:

- NMPVR = Neutrophil count / Mean Platelet Volume
- LMR = Lymphocyte count / Monocyte count
- NMR = Neutrophil count / Monocyte count
- NLR = Neutrophil count / Lymphocyte count
- HALP = (Hemoglobin × Albumin × Lymphocyte count) / Platelet count
- HPR = Hemoglobin / Platelet count
- RPR = RDW / Platelet count
- PLR = Platelet count / Lymphocyte count
- AAR = AST / ALT
- LAR = LDH / Albumin
- LLR = LDH / Lymphocyte count
- TBAR = Total Bilirubin / Albumin
- DIR = Direct Bilirubin / Indirect Bilirubin
- GLR = Glucose / Lymphocyte count
- FLR = Fibrinogen / Lymphocyte count

2.2 LMR and CA724 combined score

Receiver operating characteristic (ROC) analysis was performed based on overall survival (OS) outcomes to determine the optimal cutoff values for LMR and CA724. The combined LMR + CA724 score was defined as follows: (1) 0 points: high LMR and low CA724, (2) 2 points: low LMR and high CA724, (3) 1 point: both high or both low LMR and CA724.

2.3 Follow-up and survival definition

Overall survival (OS) was defined as the time from surgery to death from any cause. All patients were followed for a period of five years after surgery.

2.4 Statistical methods

The optimal cutoff values for LMR and CA724 were determined using ROC curves. The prognostic performance of LMR, CA724, and the LMR + CA724 score for OS was assessed. Kaplan-Meier survival analysis was used to estimate OS, with subgroup comparisons conducted using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards model to calculate hazard ratios and identify independent

prognostic factors. The Chi-square test and independent samples *t*-test were used to compare categorical and continuous variables, respectively. A prognostic nomogram was constructed based on significant variables identified in multivariate analysis. A *P*-value < 0.05 was considered statistically significant.

3 Results

3.1 Baseline characteristics of patients

A total of 313 patients were included in this study, comprising 258 males (82.4%) and 55 females (17.6%), with a median age of 61 years (range, 25-81 years). According to postoperative pathological staging, 66 patients (21.1%) were diagnosed with stage I-II disease, 99 patients (31.6%) with stage III, and 142 patients (45.4%) with stage IV. Six patients (1.9%) were classified as having incomplete or unspecified staging information (Table 1).

3.2 COX univariate analysis of inflammatory markers

Univariate analysis of all hematological indicators revealed that only LMR and CA724 were significantly associated with OS (*P* < 0.05) (Table 2).

3.3 AUC values for LMR, CA724, and LMR + CA724 scores

ROC curve analysis was used to determine the optimal cutoff values for the LMR and cancer antigen 724 (CA724), which were 2.31 and 3.7478, respectively. Based on these thresholds, patients were categorized into high and low groups for each marker.

Patients with $LMR \geq 2.31$ and $CA724 < 3.7478$ were assigned a score of 0 in the LMR + CA724 scoring system. Patients with $LMR < 2.31$ and $CA724 \geq 3.7478$ were assigned a score of 2. All other patients were assigned a score of 1. According to this scoring system, 85 patients (27.2%) were scored as 0, 163 patients (52.1%) as 1, and 65 patients (20.7%) as 2.

The area under the curve (AUC) values for predicting overall survival were as follows: (1) LMR: 0.576 (95 percent confidence interval [CI] = 0.510-0.641), (2) CA724: 0.594 (95 percent CI = 0.530-0.657), (3) LMR + CA724: 0.646 (95 percent CI = 0.590-0.702).

These results suggest that the combined LMR + CA724 score demonstrated superior prognostic accuracy compared to either marker alone (Fig. 1).

3.4 Survival analysis of LMR + CA724 score

Survival analysis demonstrated that patients in the low LMR group had a significantly poorer prognosis compared to those in the high LMR group. Similarly, patients with high CA724 levels experienced worse outcomes than those with low CA724 levels. When stratified by the LMR + CA724 score, patients in the score 2 group exhibited the worst overall survival compared to those in the score 0 and score 1 groups (Fig. 2).

3.5 Multifactorial analysis of the LMR + CA724 score

Cox univariate analysis was performed to assess the relationship between OS and the LMR + CA724 score, along with patients' general clinical data, surgical details, and pathological characteristics. The analysis revealed that the following variables were significantly associated with OS (*P* < 0.05): pTNM stage, Borrmann classification, Lauren classification, lymphovascular invasion (LVI), perineural invasion (PNI), infiltrative pattern (INF), histological type, tumor size, and LMR + CA724 score.

These variables were subsequently included in the Cox multivariate analysis. The results identified four independent prognostic factors for patients with gastric fundus cancer: (1) pTNM stage (hazard ratio [HR] = 4.18, 95% confidence interval [CI] = 1.42-12.32, *P* = 0.0039), (2) Borrmann classification (HR = 6.90, 95% CI = 1.13-42.12, *P* = 0.0365), (3) Histological type (HR = 1.98, 95% CI = 1.09-3.58, *P* = 0.0241), (4) LMR + CA724 score (HR = 3.81, 95% CI = 2.17-6.69, *P* < 0.0001).

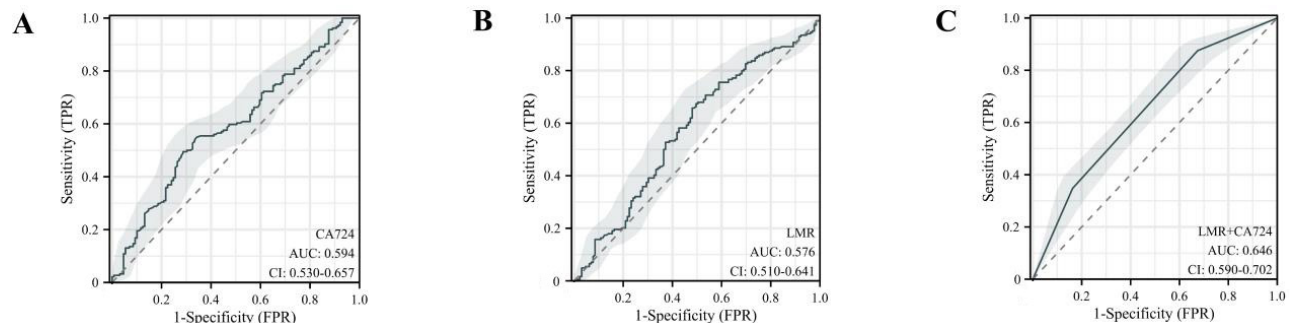


Fig. 1 ROC curves of LMR, CA724, and LMR + CA724 score for predicting overall survival. ROC, Receiver operating characteristic; LMR, lymphocyte-to-monocyte ratio

Table 1 Clinical and pathological characteristics of patients with proximal gastric cancer

Characteristics		Overall (N = 313)	Score0 (N = 85)	Score1 (N = 163)	Score2 (N = 65)	P value
Sex (%)	Male	258 (82.4)	68 (80.0)	134 (82.2)	56 (86.2)	0.614
	Female	55 (17.6)	17 (20.0)	29 (17.8)	9 (13.8)	
Age (median [IQR])		61.00 [53.00, 66.00]	60.00 [52.00, 65.00]	60.00 [52.00, 65.00]	64.00 [56.00, 70.00]	0.010
BMI (median [IQR])		23.39 [21.45, 25.04]	24.06 [21.45, 25.95]	22.86 [21.37, 24.71]	23.29 [21.30, 24.61]	0.069
pTNM (%)	I	66 (21.1)	28 (32.9)	29 (17.8)	9 (13.8)	0.006
	II	99 (31.6)	30 (35.3)	53 (32.5)	16 (24.6)	
	III	142 (45.4)	27 (31.8)	77 (47.2)	38 (58.5)	
	IV	6 (1.9)	0 (0.0)	4 (2.5)	2 (3.1)	
Borrmann (%)	0	45 (14.4)	17 (20.0)	23 (14.1)	5 (7.7)	0.267
	I	20 (6.4)	6 (7.1)	10 (6.1)	4 (6.2)	
	II	53 (16.9)	19 (22.4)	25 (15.3)	9 (13.8)	
	III	176 (56.2)	40 (47.1)	95 (58.3)	41 (63.1)	
Lauren (%)	Intestinal	147 (47.0)	37 (43.5)	73 (44.8)	37 (56.9)	0.351
	Mixed	115 (36.7)	35 (41.2)	63 (38.7)	17 (26.2)	
	Diffuse	51 (16.3)	13 (15.3)	27 (16.6)	11 (16.9)	
LVI (%)	Positive	158 (50.5)	52 (61.2)	82 (50.3)	24 (36.9)	0.013
	Negative	155 (49.5)	33 (38.8)	81 (49.7)	41 (63.1)	
PNI (%)	Positive	77 (24.6)	27 (31.8)	37 (22.7)	13 (20.0)	0.182
	Negative	236 (75.4)	58 (68.2)	126 (77.3)	52 (80.0)	
Mesenchyme (%)	Medullary	33 (10.5)	7 (8.2)	17 (10.4)	9 (13.8)	0.528
	Intermediate	245 (78.3)	71 (83.5)	124 (76.1)	50 (76.9)	
	scirrhous	35 (11.2)	7 (8.2)	22 (13.5)	6 (9.2)	
INF (%)	INFa	108 (34.5)	25 (29.4)	60 (36.8)	23 (35.4)	0.731
	INFb	121 (38.7)	34 (40.0)	60 (36.8)	27 (41.5)	
	INFc	84 (26.8)	26 (30.6)	43 (26.4)	15 (23.1)	
HER2 (%)	0	157 (50.2)	47 (55.3)	83 (50.9)	27 (41.5)	0.300
	1 +	108 (34.5)	28 (32.9)	53 (32.5)	27 (41.5)	
	2 +	30 (9.6)	4 (4.7)	20 (12.3)	6 (9.2)	
	3 +	18 (5.8)	6 (7.1)	7 (4.3)	5 (7.7)	
chemotherapy (%)	no	175 (55.9)	51 (60.0)	83 (50.9)	41 (63.1)	0.167
	yes	138 (44.1)	34 (40.0)	80 (49.1)	24 (36.9)	
Histological.type (%)	High-moderately	163 (52.1)	47 (55.3)	77 (47.2)	39 (60.0)	0.444
	poorly	94 (30.0)	20 (23.5)	56 (34.4)	18 (27.7)	
	low adhesion	48 (15.3)	15 (17.6)	26 (16.0)	7 (10.8)	
	mucinous adenocarcinoma	8 (2.6)	3 (3.5)	4 (2.5)	1 (1.5)	
Tumor.size (median [IQR])		50.00 [30.00, 60.00]	40.00 [25.00, 55.00]	45.00 [30.00, 60.00]	55.00 [40.00, 80.00]	<0.001
NMPVR (median [IQR])		0.41 [0.32, 0.53]	0.38 [0.29, 0.46]	0.41 [0.33, 0.52]	0.47 [0.35, 0.61]	0.006
NMR (median [IQR])		8.41 [6.90, 10.00]	8.88 [7.24, 10.07]	8.48 [7.04, 10.12]	7.65 [6.43, 8.80]	0.007
NLR (median [IQR])		2.04 [1.54, 2.77]	1.70 [1.30, 2.25]	1.91 [1.53, 2.75]	2.91 [2.23, 3.54]	<0.001
MWR (median [IQR])		0.07 [0.06, 0.08]	0.07 [0.06, 0.07]	0.07 [0.06, 0.08]	0.09 [0.08, 0.09]	<0.001
HALP (median [IQR])		42.28 [25.37, 60.08]	47.60 [35.09, 66.91]	45.33 [28.52, 60.65]	26.07 [19.94, 42.14]	<0.001
HPR (median [IQR])		0.57 [0.41, 0.71]	0.59 [0.44, 0.69]	0.58 [0.41, 0.72]	0.51 [0.33, 0.65]	0.063
RPR (median [IQR])		0.06 [0.05, 0.07]	0.06 [0.05, 0.07]	0.06 [0.05, 0.07]	0.06 [0.05, 0.07]	0.723

Continued

Table 1 Continued

Characteristics	Overall (N = 313)	Score0 (N = 85)	Score1 (N = 163)	Score2 (N = 65)	P value
PLR (median [IQR])	125.62 [98.11, 170.11]	115.82 [89.22, 137.16]	123.40 [97.44, 163.60]	173.83 [132.54, 212.29]	< 0.001
AAR (median [IQR])	1.12 [0.88, 1.33]	1.13 [0.88, 1.33]	1.03 [0.87, 1.27]	1.21 [1.06, 1.55]	0.012
LAR (median [IQR])	3.79 [3.45, 4.36]	3.77 [3.40, 4.38]	3.76 [3.48, 4.26]	3.89 [3.46, 4.53]	0.629
LLR (median [IQR])	83.54 [65.47, 105.11]	73.86 [60.93, 89.63]	83.24 [64.21, 104.44]	99.38 [80.72, 125.62]	< 0.001
TBAR (median [IQR])	0.26 [0.21, 0.36]	0.26 [0.20, 0.35]	0.27 [0.21, 0.36]	0.26 [0.21, 0.37]	0.775
DIR (median [IQR])	0.57 [0.46, 0.68]	0.57 [0.46, 0.66]	0.56 [0.45, 0.69]	0.60 [0.49, 0.71]	0.207
GLR (median [IQR])	2.83 [2.24, 3.56]	2.52 [2.03, 3.03]	2.76 [2.16, 3.57]	3.39 [2.62, 4.27]	< 0.001
FAR (median [IQR])	0.08 [0.06, 0.09]	0.07 [0.06, 0.08]	0.07 [0.06, 0.09]	0.09 [0.07, 0.10]	< 0.001
FLR (median [IQR])	1.66 [1.23, 2.15]	1.38 [1.05, 1.77]	1.54 [1.23, 2.07]	2.15 [1.82, 2.72]	< 0.001

IQR, Interquartile range; NMPVR, Neutrophil count / Mean Platelet Volume; LMR, Lymphocyte count / Monocyte count; NMR, Neutrophil count / Monocyte count; NLR, Neutrophil count / Lymphocyte count; HALP, (Hemoglobin \times Albumin \times Lymphocyte count) / Platelet count; HPR, Hemoglobin / Platelet count; RPR, RDW / Platelet count; PLR, Platelet count / Lymphocyte count; AAR, AST / ALT; LAR, LDH / Albumin; LLR, LDH / Lymphocyte count; TBAR, Total Bilirubin / Albumin; DIR, Direct Bilirubin / Indirect Bilirubin; GLR, Glucose / Lymphocyte count; FLR, Fibrinogen / Lymphocyte count.

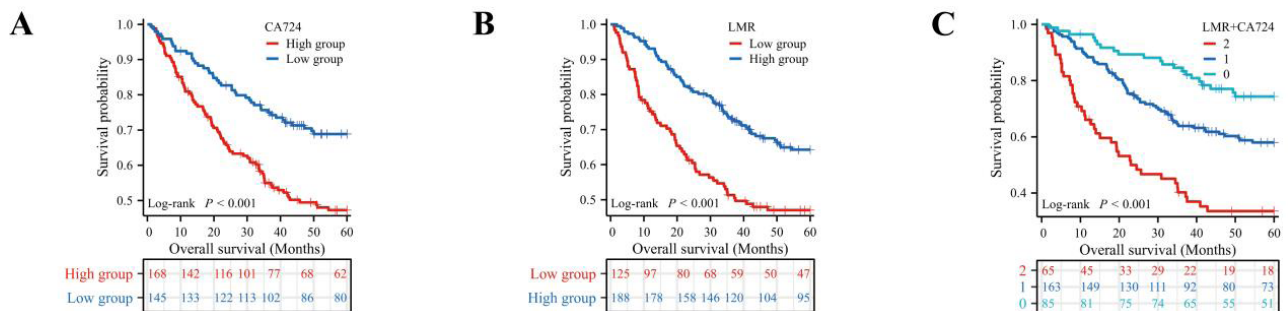


Fig. 2 Kaplan-Meier survival curves based on LMR, CA724, and LMR + CA724 score. LMR, lymphocyte-to-monocyte ratio

These findings suggest that the LMR + CA724 score, along with key clinical and pathological features, serves as a strong independent predictor of overall survival in patients with proximal gastric cancer.

3.6 Subgroup analysis

To further evaluate the prognostic value of the LMR + CA724 score in patients with gastric fundus cancer, survival analyses were conducted across several clinically relevant subgroups. These included stratification by pTNM stage (I + II versus III + IV), Borrmann classification (Borrmann type IV versus non-Borrmann type IV), and histological differentiation (high to moderate differentiation, poorly differentiated adenocarcinoma, and signet-ring cell carcinoma).

The results showed that, except in the Borrmann type IV subgroup, patients with an LMR + CA724 score of 2 consistently exhibited significantly worse overall survival compared to those with scores of 0 or 1 (all $P < 0.05$). Although statistical significance was not reached in the Borrmann type IV subgroup, the median survival time for patients with an LMR + CA724 score of 2 was markedly shorter than that of patients with scores of 1 and 0 (4.6

months versus 21.8 months versus 19.8 months, respectively), indicating a clear trend toward poorer outcomes (Fig. 3).

3.7 Correlation between LMR + CA724 score and clinicopathological features

The LMR + CA724 score of 2 was found to be significantly associated with several adverse clinicopathological features, including older age, more advanced pTNM staging, presence of vascular cancer thrombus, higher neutrophil-to-mean platelet volume ratio (NMPVR), higher neutrophil-to-monocyte ratio (NMR), and higher aspartate aminotransferase-to-alanine aminotransferase ratio (AAR). These associations suggest that a high LMR + CA724 score reflects a more aggressive disease phenotype.

3.8 Prognostic nomogram for OS in proximal gastric cancer

Based on the results of multivariate analysis, four independent prognostic indicators, pTNM stage, Borrmann classification, histological type, and the LMR + CA724 score, were incorporated into a prognostic nomogram to predict overall survival in patients with proximal gastric cancer. The area under the curve (AUC) of

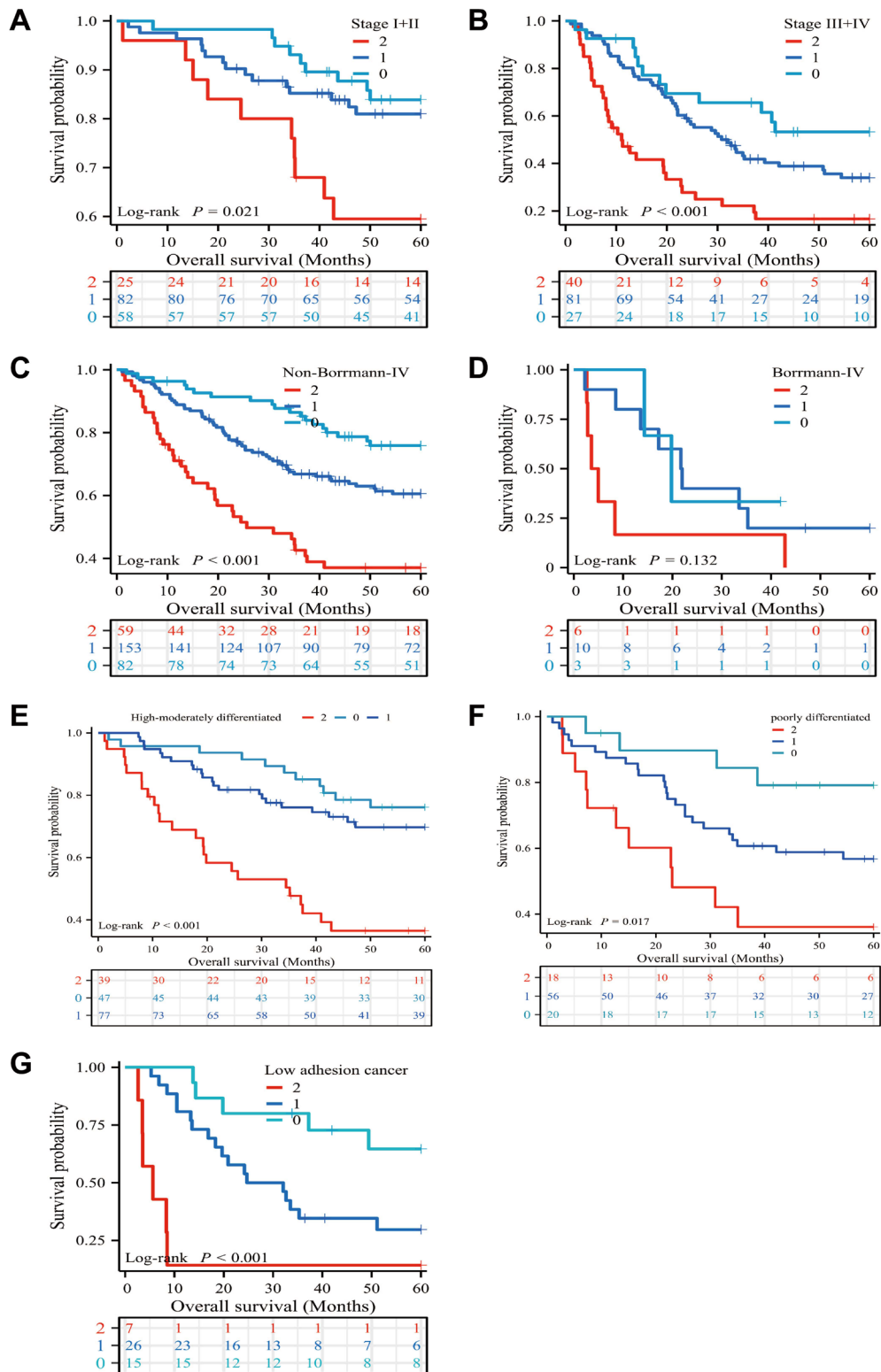


Fig. 3 Subgroup analysis of combined scoring

(A) Stage I-II; (B) Stage III-IV; (C) Non-Borrmann IV; (D) Borrmann IV; (E) High-moderately differentiated; (F) Poorly differentiated; (G) Low adhesion cancer.

Table 2 Univariate Cox analysis of hematological markers associated with overall survival

Characteristics	Univariate analysis		Multivariate analysis		Characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value		OR (95% CI)	P value	OR (95% CI)	P value
Sex					Mesenchyme				
Male	Reference		(reference)		medullary type	Reference		Reference	
Female	1.18 (0.76-1.83)	0.457	NA	NA	intermedius type	0.76 (0.46-1.28)	0.304	NA	NA
Age	1.02 (1-1.04)	0.063	NA	NA	hard type	0.94 (0.47-1.85)	0.852	NA	NA
BMI	0.96 (0.91-1.02)	0.196	NA	NA	INF				
pTNM					INFa	Reference		Reference	
I	Reference		Reference		INFb	0.73 (0.47-1.14)	0.169	0.71 (0.43-1.17)	0.1781
II	3.51 (1.45-8.48)	0.005	1.45 (0.5-4.24)	0.4937	INFc	1.86 (1.23-2.79)	0.003	1.08 (0.65-1.79)	0.7679
III	11.94 (5.21-27.35)	0	4.18 (1.42-12.32)	0.0095	HER-2				
IV	24.63 (7.47-81.23)	0	8.53 (1.99-36.56)	0.0039	0	Reference		Reference	
Lauren classification					1 +	0.91 (0.62-1.33)	0.617	NA	NA
Intestinal	Reference		Reference		2 +	0.82 (0.43-1.55)	0.540	NA	NA
Mixed	0.93 (0.62-1.38)	0.711	0.96 (0.56-1.66)	0.8861	3 +	1.28 (0.66-2.49)	0.463	NA	NA
Diffuse	1.59 (1.01-2.49)	0.045	1.42 (0.82-2.44)	0.2069	Chemotherapy				
Borrmann type					No	Reference		Reference	
Borrmann0	Reference		Reference		Yes	0.98 (0.69-1.39)	0.905	NA	NA
Borrmann I	11.62 (2.47-54.75)	0.002	5.27 (0.9-30.72)	0.0649	Histology				
Borrmann II	9.12 (2.12-39.33)	0.003	3.39 (0.6-19.33)	0.1685	High-moderately	Reference		Reference	
Borrmann III	15.47 (3.8-62.9)	0	4.36 (0.78-24.23)	0.0927	poorly	1.27 (0.84-1.91)	0.252	1.12 (0.7-1.78)	0.6378
Borrmann IV	43.52 (9.97-189.87)	0	6.9 (1.13-42.12)	0.0365	low adhesion	2.18 (1.39-3.41)	0.001	1.98 (1.09-3.58)	0.0241
Lymphovascular invasion (LVI)					mucinous adenocarcinoma	1.73 (0.63-4.76)	0.291	1.69 (0.57-5.02)	0.3418
no	Reference		Reference		LMR + CA724				
yes	1.79 (1.26-2.54)	0.001	0.74 (0.48-1.14)	0.1778	0	Reference		Reference	
PNI					1	1.89 (1.16-3.1)	0.011	1.42 (0.85-2.37)	0.1753
no	Reference		Reference		2	4.19 (2.48-7.09)	< 0.001	3.81 (2.17-6.69)	< 0.001
yes	2.17 (1.35-3.5)	0.001	1.17 (0.68-2.04)	0.5715	Tumor.size (median [IQR])	1.02 (1.01-1.03)	< 0.001	1 (0.99-1.01)	0.5693

BMI, body mass index; PNI, perineural invasion; INF, infiltrative pattern; HER-2, human epidermal growth factor receptor 2; LMR, lymphocyte-to-monocyte ratio; NA, Not available.

the nomogram was 0.817, indicating strong predictive accuracy. Additionally, both the decision curve analysis and the calibration plot demonstrated the model's clinical utility and consistency in predicting survival outcomes (Fig. 4).

4 Discussion

Over the years, the intricate relationship between inflammation and cancer has played a critical role in guiding the prevention and treatment of inflammation-related malignancies such as liver and gastric cancers^[12-13]. Inflammatory markers including the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) have been extensively investigated in various malignancies, offering practical prognostic insight for clinicians^[14-15]. Likewise, tumor markers such as CA724 have demonstrated diagnostic and prognostic value in multiple clinical settings^[16].

In this study, which focused on patients with proximal gastric cancer residing in extremely cold regions, Cox univariate analysis

identified only the LMR and CA724 as statistically significant prognostic indicators. Based on this finding, these two markers were combined to develop the LMR + CA724 score. To the best of our knowledge, this is the first investigation of the prognostic significance of the preoperative LMR + CA724 score in this specific patient population. Our results show that an elevated preoperative LMR + CA724 score is associated with a poorer prognosis. Furthermore, subgroup analyses revealed that this score effectively stratifies patient outcomes across different TNM stages, Borrmann classification groups, and histological subtypes.

The prognostic impact of LMR may be explained by the role of lymphocytes and monocytes in tumor immunity and progression. Lymphocytes contribute to antitumor activity through cytotoxic effects and immune surveillance. Tumor-infiltrating lymphocytes can induce apoptosis in tumor cells, and growing evidence supports the role of lymphocytes as essential cellular components in immune-mediated tumor suppression^[17-18]. A reduction in lymphocyte count may impair immune responses, in

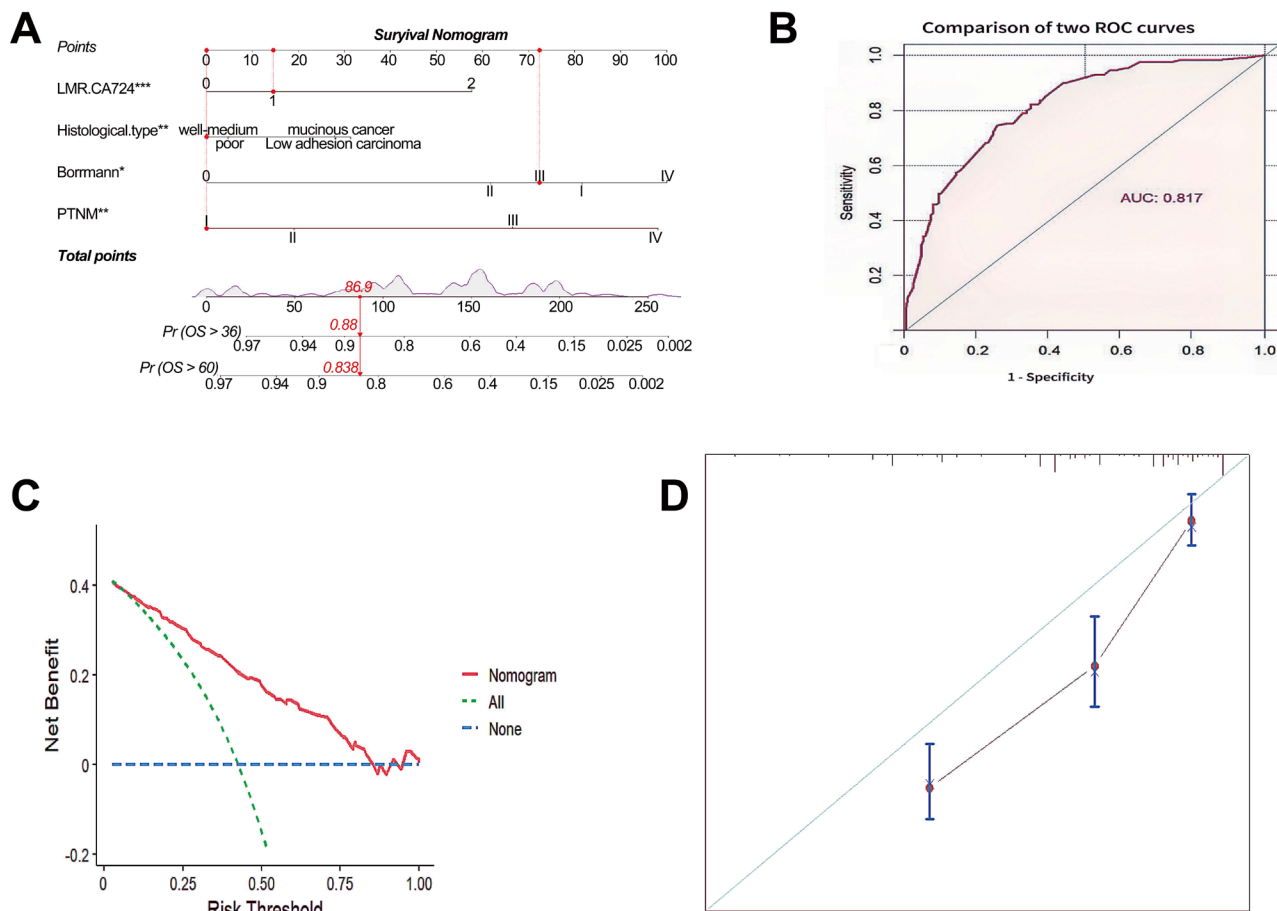


Fig. 4 Prognostic nomogram for overall survival and corresponding calibration and decision curve analyses

(A) Nomogram predicting 5-year survival; (B) ROC analysis of nomogram predicting 5-year mortality rate; (C) Decision curve analysis of nomogram; (D) calibration curve of nomogram.

part by promoting the release of immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF- β)^[19]. Conversely, monocytes play a pro-tumorigenic role. They are actively recruited to the tumor microenvironment in response to tumor-derived signals such as CCL5, and can differentiate into tumor-associated macrophages (TAMs), which suppress immune surveillance and facilitate tumor growth, invasion, and metastasis^[20-23]. The LMR thus reflects a balance between antitumor immunity and tumor-promoting inflammation, making it a reliable prognostic indicator across multiple malignancies^[24-25]. CA724 is a high-molecular-weight, mucin-like glycoprotein that is upregulated in gastrointestinal, reproductive, and pulmonary malignancies. It is widely used in clinical practice for the diagnosis, monitoring, and prognostic evaluation of gastrointestinal cancers^[26-27].

In this study, the combined LMR + CA724 score demonstrated

a higher AUC than either LMR or CA724 alone, indicating superior prognostic accuracy for patients with proximal gastric cancer. Furthermore, this score functioned as an independent prognostic factor. Clinically, patients with elevated LMR + CA724 scores should be monitored closely and may benefit from more aggressive postoperative adjuvant chemotherapy and follow-up.

Nonetheless, several limitations must be acknowledged. First, this was a single-center, retrospective study, which may introduce selection and reporting biases. Future studies should aim to use multicenter, prospective designs to improve the generalizability of these findings. Second, although OS is a widely accepted endpoint, this study lacked sufficient data on disease-free survival (DFS), which limited our ability to assess long-term recurrence risk. Therefore, additional prospective studies with comprehensive clinicopathological and survival data are needed to validate and refine the utility of the LMR + CA724 score.

5 Conclusion

In this study of patients with proximal gastric cancer from a cold climate region, we identified that the preoperative combination of the lymphocyte-to-monocyte ratio and CA724 (LMR + CA724) serves as a robust and independent predictor of overall survival. Elevated LMR + CA724 scores were significantly associated with worse outcomes across diverse clinical subgroups. This combined score offers a practical and cost-effective tool to support individualized prognostic assessment and guide treatment planning. Future multicenter, prospective studies are warranted to confirm these findings and further establish the clinical applicability of the LMR + CA724 score in gastric cancer management.

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Research ethics

This study was approved by the Ethics Committee of Harbin Medical University Cancer Hospital (2019-164-R). The study was conducted in accordance with the ethical standards set out in the 1964 Declaration of Helsinki and its later amendments.

Informed consent

Not applicable.

Author contributions

Zhu X Q, Li Q L, and Liang S S designed and conceptualized the study, drafted the manuscript, and contributed equally to this work. Zhu X Q was responsible for data collection. Song H B and Wu H X performed the final review and revision of the manuscript. All authors contributed to the article and approved the final version for publication.

Use of large language models AI and Machine Learning tools

Not applicable.

Conflict of interest

The authors declare no conflicts of interest related to this study.

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Data availability

Patient data were stored in the Gastric Cancer Information Management System v1.2, developed by Harbin Medical University Cancer Hospital (Copyright No. 2013SR087424, <http://www.sghmu.com>).

References

- [1] Erratum: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 2020; 70(4): 313.
- [2] Soerjomataram I, Lortet-Tieulent J, Parkin D M, *et al*. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet*, 2012; 380(9856): 1840-1850.
- [3] Botterweck AA, Schouten L J, Volovics A, *et al*. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. *Int J Epidemiol*, 2000; 29(4): 645-654.
- [4] Huang Q, Shi J, Sun Q, *et al*. Clinicopathological characterisation of small (2cm or less) proximal and distal gastric carcinomas in a Chinese population. *Pathology*, 2015; 47(6): 526-532.
- [5] Parfitt J R, Miladinovic Z, Driman D K. Increasing incidence of adenocarcinoma of the gastroesophageal junction and distal stomach in Canada -- an epidemiological study from 1964-2002. *Can J Gastroenterol*, 2006; 20(4): 271-276.
- [6] Wang X, Liu F, Li Y, *et al*. Comparison on clinicopathological features, treatments and prognosis between proximal gastric cancer and distal gastric cancer: a national cancer data base analysis. *J Cancer*, 2019; 10(14): 3145-3153.
- [7] Röcken C, Behrens H M. Validating the prognostic and discriminating value of the TNM-classification for gastric cancer - a critical appraisal. *Eur J Cancer*, 2015; 51(5): 577-586.
- [8] Pan Y C, Jia Z F, Cao D H, *et al*. Preoperative lymphocyte-to-monocyte ratio (LMR) could independently predict overall survival of resectable gastric cancer patients. *Medicine (Baltimore)*, 2018; 97(52): e13896.
- [9] Duzkopru Y, Kocanoglu A, Dogan O, *et al*. Hemoglobin, albumin, lymphocyte, and platelet score as a predictor of prognosis in metastatic gastric cancer. *World J Gastrointest Oncol*, 2023; 15(9): 1626-1635.
- [10] Hannarici Z, Yilmaz A, Buyukbayram M E, *et al*. The value of pretreatment glucose-to-lymphocyte ratio for predicting survival of metastatic gastric cancer. *Future Oncol*, 2023; 19(4): 315-325.
- [11] Chandra R, Balachandar N, Wang S, *et al*. The changing face of

- gastric cancer: epidemiologic trends and advances in novel therapies. *Cancer Gene Ther*, 2021; 28(5): 390-399.
- [12] Penta R, De Falco M, Iaquinto G, *et al.* Helicobacter pylori and gastric epithelial cells: from gastritis to cancer. *J Exp Clin Cancer Res*, 2005; 24(3): 337-345.
- [13] Sun B, Karin M. Obesity, inflammation, and liver cancer. *J Hepatol*, 2012; 56(3): 704-713.
- [14] Ye Z, Yu P, Cao Y, *et al.* Prediction of peritoneal cancer index and prognosis in peritoneal metastasis of gastric cancer using NLR-PLR-DDI score: a retrospective study. *Cancer Manag Res*, 2022; 14: 177-187.
- [15] Shi X, Li S, Wang Y, *et al.* Predictive value of platelet-to-lymphocyte ratio combined with CA199 levels in postoperative survival of patients with gastric cancer: A retrospective study. *Int Immunopharmacol*, 2023; 124(Pt B): 110987.
- [16] Gong X, Zhang H. Diagnostic and prognostic values of anti-helicobacter pylori antibody combined with serum CA724, CA19-9, and CEA for young patients with early gastric cancer. *J Clin Lab Anal*, 2020; 34(7): e23268.
- [17] Kang M, Jeong C W, Kwak C, *et al.* Preoperative neutrophil-lymphocyte ratio can significantly predict mortality outcomes in patients with non-muscle invasive bladder cancer undergoing transurethral resection of bladder tumor. *Oncotarget*, 2017; 8(8): 12891-12901.
- [18] Fridman W H, Pagès F, Sautès-Fridman C, *et al.* The immune contexture in human tumours: impact on clinical outcome. *Nat Rev Cancer*, 2012; 12(4): 298-306.
- [19] Salazar-Onfray F, López M N, Mendoza-Naranjo A. Paradoxical effects of cytokines in tumor immune surveillance and tumor immune escape. *Cytokine Growth Factor Rev*, 2007; 18(1-2): 171-182.
- [20] Wilcox R A, Wada D A, Ziesmer S C, *et al.* Monocytes promote tumor cell survival in T-cell lymphoproliferative disorders and are impaired in their ability to differentiate into mature dendritic cells. *Blood*, 2009; 114(14): 2936-2944.
- [21] Peng L S, Zhang J Y, Teng Y S, *et al.* Tumor-associated monocytes/macrophages impair NK-Cell function via TGFβ1 in human gastric cancer. *Cancer Immunol Res*, 2017; 5(3): 248-256.
- [22] Mantovani A, Schioppa T, Porta C, *et al.* Role of tumor-associated macrophages in tumor progression and invasion. *Cancer Metastasis Rev*, 2006; 25(3): 315-322.
- [23] Mantovani A, Allavena P, Sica A, *et al.* Cancer-related inflammation. *Nature*, 2008; 454(7203): 436-444.
- [24] Toyokawa T, Kubo N, Tamura T, *et al.* The pretreatment Controlling Nutritional Status (CONUT) score is an independent prognostic factor in patients with resectable thoracic esophageal squamous cell carcinoma: results from a retrospective study. *BMC Cancer*, 2016; 16(1): 722.
- [25] Chan J C, Chan D L, Diakos C I, *et al.* The lymphocyte-to-monocyte ratio is a superior predictor of overall survival in comparison to established biomarkers of resectable colorectal cancer. *Ann Surg*, 2017; 265(3): 539-546.
- [26] Chen X Z, Zhang W K, Yang K, *et al.* Correlation between serum CA724 and gastric cancer: multiple analyses based on Chinese population. *Mol Biol Rep*, 2012; 39(9): 9031-9039.
- [27] Liang Y, He M, Fan X, *et al.* An abnormal elevation of serum CA72-4 by ganoderma lucidum spore powder. *Ann Clin Lab Sci*, 2013; 43(3): 337-340.